



Journal of Research in Allied Life Sciences

Contents available at: <https://www.swamivivekanandauniversity.ac.in/jrals/>

MicroRNA-Protein Interaction Networks in Down Syndrome-Linked Alzheimer's Pathogenesis: A Compact Review

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Abstract

Individuals with Down syndrome (DS) face near-universal risk of developing Alzheimer's disease (AD) pathology by mid-life, driven by chromosome 21 gene dosage effects. This review synthesizes emerging evidence on microRNA (miRNA)-protein regulatory networks that underlie accelerated AD progression in DS, with emphasis on extracellular vesicle (EV)-derived molecular signatures. Dysregulated miRNAs—including inflammatory miR-155 and miR-146a, and chromosome 21-encoded miR-802—converge on pathways governing amyloid processing, tau phosphorylation, synaptic integrity, and insulin signaling. Integrated analyses reveal miR-155 as a central regulatory hub linking neuroinflammation to neuronal insulin resistance, a mechanism validated in cellular models. EV-based miRNA/protein profiling offers minimally invasive biomarker potential for early AD detection in DS and identifies actionable therapeutic targets for disease modification.

Keywords: Down syndrome, Alzheimer's disease, microRNA, extracellular vesicles, neuroinflammation, insulin signaling, biomarkers

1. Introduction

Down syndrome, caused by trisomy 21, confers exceptionally high lifetime risk for Alzheimer's disease, with virtually all individuals developing AD neuropathology by their fifth decade (Lott and Dierssen, 2010). This accelerated trajectory stems primarily from lifelong overexpression of the amyloid precursor protein (APP) gene located on chromosome 21, resulting in excessive amyloid- β (A β) production and deposition (Lott and Head, 2019). However, AD pathogenesis in DS extends beyond APP triplication to encompass dysregulation of other chromosome 21 genes, altered immune signaling, mitochondrial dysfunction, and perturbations in non-coding RNA networks (Sukreet et al., 2024).

MicroRNAs are small (~22 nucleotide) non-coding RNAs that post-transcriptionally regulate gene expression by binding target mRNAs, leading to translational repression or degradation (Hébert and De Strooper, 2009). Several miRNA genes reside on chromosome 21 (including miR-99a, miR-125b-2, and miR-802), and their dosage imbalance

in DS may contribute to pathological cascades converging on AD-relevant processes (Pérez-Villarreal et al., 2022; Zeng et al., 2025). Extracellular vesicles—membrane-bound nanoparticles secreted by cells—transport miRNAs and proteins through biological fluids, can traverse the blood-brain barrier, and serve as carriers of pathological signals in neurodegenerative disease (Vlassov et al., 2012; Ramos-Zaldívar et al., 2022). Plasma-derived EVs thus represent an accessible window into brain molecular pathology, enabling biomarker discovery and mechanistic investigation (Bravo-Miana et al., 2024; Park et al., 2024).

This review examines the evidence linking miRNA dysregulation in DS to accelerated AD, focusing on EV-mediated miRNA-protein regulatory networks, inflammatory-metabolic crosstalk, and translational implications for early detection and therapeutic intervention.

Chromosome 21 Gene Dosage and Alzheimer's Pathogenesis

APP Overexpression and Amyloid Cascade

Triplication of APP drives chronic overproduction of A β peptides, which aggregate into oligomers and plaques that trigger synaptic dysfunction, tau hyperphosphorylation, and neurodegeneration (Lott and Head, 2019). However, APP-centric mechanisms alone do not fully explain the multifaceted AD pathology observed in DS.

Non-APP Chromosome 21 Contributors

Recent genetic and functional studies have identified additional chromosome 21 genes that modulate AD risk, including DYRK1A (involved in tau phosphorylation and alternative splicing), RCAN1 (regulator of calcineurin/NFAT signaling), and several miRNA genes (Tosh et al., 2021; Sukreet et al., 2024). These genes influence inflammatory responses, endosomal-lysosomal trafficking, oxidative stress, and synaptic homeostasis, creating a multi-layered vulnerability that accelerates neurodegeneration beyond what would be expected from APP overexpression alone (Lott and Head, 2019).

MicroRNA Dysregulation in Down Syndrome and Alzheimer's Disease

Chromosome 21-Encoded miRNAs

Chromosome 21 harbors a cluster of miRNA genes whose triplication results in constitutive overexpression in DS. miR-802, for example, is consistently upregulated in DS tissues and plasma EVs and is predicted to target genes involved in neuronal signaling and glucose metabolism (Pérez-Villarreal et al., 2022). Network analyses implicate chromosome 21 miRNAs in broad regulatory circuits affecting synaptic function, proteostasis, and metabolic pathways—effects that may compound APP-driven toxicity (Zeng et al., 2025).

Inflammatory miRNAs: miR-155 and miR-146a

miR-155 and miR-146a are central regulators of innate immunity and neuroinflammation, modulating toll-like receptor signaling, cytokine production, and microglial activation (Aslani et al., 2021). Both are elevated in AD brain tissue and peripheral biofluids (Pascua-Maestro et al., 2019). miR-155, in particular, has been implicated in microglial-mediated synaptic pruning, modulation of A β phagocytosis, and suppression of insulin signaling pathways (Jankauskas et al., 2021; Catanzaro et al., 2023). Conditional deletion of miR-155 in microglia reveals context-dependent effects on synaptic integrity and neuroinflammation, underscoring its complex role in CNS homeostasis (Aloi et al., 2023).

miR-146a dysregulation impacts energy metabolism and mitochondrial function during neuroinflammatory stress, potentially linking immune activation to metabolic dysfunction in neurons (Kim et al., 2021). The convergence of these inflammatory miRNAs with chromosome 21 miRNA dosage effects may create a synergistic pathogenic environment in DS-associated AD.

Extracellular Vesicles as Mediators and Biomarkers

EV Biology and Blood-Brain Barrier Crossing

EVs, including exosomes (30-150 nm) and microvesicles, are released by neurons, astrocytes, and microglia and can cross the blood-brain barrier bidirectionally (Ramos-Zaldívar et al., 2022). They encapsulate and stabilize cargo—including miRNAs, proteins, lipids, and nucleic acids—facilitating intercellular communication and potentially propagating pathological signals such as aggregated A β and tau species (Vlassov et al., 2012; Shahlai et al., 2025).

CNS-Derived EVs in Peripheral Blood

Methodological advances now enable enrichment of neuron- or glia-derived EV subpopulations from plasma using immunocapture strategies targeting cell-type-specific surface markers (Bravo-Miana et al., 2024). Profiling these CNS-derived EVs provides a minimally invasive approach to monitor brain molecular pathology, with demonstrated utility in AD biomarker research (Pham et al., 2024; Park et al., 2024).

EV miRNA and Protein Signatures in DS and AD

Small RNA sequencing and quantitative proteomics of plasma EVs from DS and AD cohorts have revealed distinct molecular signatures. Studies report upregulation of inflammatory miRNAs (miR-155, miR-146a), chromosome 21 miRNAs (miR-802), and alterations in proteins related to amyloid processing (APP, BACE1), tau phosphorylation (GSK3 β), synaptic function (synaptophysin, PSD-95), and insulin signaling (IRS1, IGF1R) (Pham et al., 2024). These signatures correlate with cognitive status and neuropathological burden, supporting their potential as prognostic and monitoring biomarkers.

Integrated miRNA-Protein Networks: Mechanistic Insights

Network Construction and Hub Identification

Integration of miRNA expression data with proteomic profiles, guided by predicted and validated miRNA-target interactions, enables construction of regulatory networks that map functional relationships. In DS-associated AD, such networks consistently identify miR-155 and miR-802 as central hubs with extensive connectivity to proteins governing inflammation, metabolism, and synaptic integrity (Zeng et al., 2025).

Pathway Enrichment: Converging on Core AD Mechanisms

Pathway enrichment analyses of miRNA-protein networks implicate dysregulated modules in:

- **Amyloid processing:** Alterations in APP, BACE1, and ADAM10 expression and activity
- **Tau phosphorylation:** Modulation of kinases (GSK3 β , CDK5) and phosphatases
- **Synaptic transmission:** Changes in pre- and post-synaptic proteins (synaptophysin, PSD-95, synaptotagmin)
- **Insulin/IGF signaling:** Downregulation of IRS1, IGF1R, and downstream PI3K/AKT pathway components

These pathways align closely with established AD mechanisms and suggest that miRNA dysregulation in DS creates a coordinated disruption of multiple neuroprotective and homeostatic systems (De la Monte and Tong, 2014).

miR-155 and Neuronal Insulin Resistance

Insulin Signaling in the Brain and AD

Impaired brain insulin signaling—often termed "type 3 diabetes"—is increasingly recognized as a core feature of AD pathophysiology, contributing to synaptic dysfunction, impaired glucose metabolism, tau hyperphosphorylation, and A β accumulation (De la Monte and Tong, 2014). Insulin resistance in neurons disrupts energy metabolism and compromises synaptic plasticity mechanisms underlying learning and memory.

miR-155 as a Regulator of Insulin Signaling

miR-155 has been shown to target components of the insulin signaling pathway, including IRS1 and IGF1R (Jankauskas et al., 2021; Catanzaro et al., 2023). EV profiling studies report strong inverse correlations between miR-155 abundance and levels of insulin signaling proteins in DS and AD cohorts. Functional validation in neuronal cell models (e.g., SH-SY5Y neuroblastoma cells) demonstrates that miR-155 overexpression reduces insulin-stimulated phosphorylation of IRS1 (Tyr612) and AKT (Ser473), recapitulating an insulin resistance phenotype (Jankauskas et al., 2021).

Linking Neuroinflammation to Metabolic Dysfunction

miR-155 upregulation in microglia and peripheral immune cells—driven by inflammatory stimuli such as A β oligomers, cytokines, and toll-like receptor activation—may propagate metabolic dysfunction to neurons via EV-mediated transfer. This creates a vicious cycle wherein neuroinflammation $\rightarrow$ miR-155 elevation $\rightarrow$ neuronal insulin resistance $\rightarrow$ synaptic dysfunction $\rightarrow$ further A β /tau pathology $\rightarrow$ amplified inflammation (Aloi et al., 2023; Huang et al., 2024).

Therapeutic Implications

miRNA-Targeted Interventions

The identification of miR-155 and other dysregulated miRNAs as mechanistic hubs suggests potential therapeutic strategies. Chemically modified antisense oligonucleotides (anti-miRs) that sequester and inhibit target miRNAs have shown efficacy in preclinical models of neuroinflammation and metabolic disease (Huang et al., 2024). Alternatively, miRNA sponges and decoys—expressed or synthetic RNA sequences containing multiple miRNA binding sites—can act as competitive inhibitors to reduce the effective concentration of pathogenic miRNAs. Modulation of upstream drivers that control miRNA expression, such as targeting inflammatory pathways including the NLRP3 inflammasome or toll-like receptor signaling cascades that drive miR-155 transcription, may offer indirect therapeutic benefit. However, cell-type-specific delivery remains a critical challenge, as miRNAs exhibit context-dependent functions across different CNS cell types, with the same miRNA potentially exerting neuroprotective effects in one cellular context while promoting pathology in another (Aloi et al., 2023).

Targeting Insulin Signaling Pathways

Strategies to restore neuronal insulin sensitivity represent a complementary therapeutic approach that addresses the metabolic dimension of DS-associated AD. Intranasal insulin delivery, which bypasses systemic circulation to directly target the CNS, has demonstrated cognitive benefits in some AD clinical trials. Insulin sensitizers such as GLP-1

receptor agonists, along with direct modulators of the PI3K/AKT pathway, have shown promise in preclinical and early clinical studies. These interventions may be particularly relevant for DS-associated AD given the robust metabolic signature—including downregulation of IRS1 and IGF1R—observed in EV profiling studies, which suggests that insulin resistance is a prominent feature of neuronal dysfunction in this population (De la Monte and Tong, 2014).

EV-Based Therapeutics

Engineered EVs loaded with therapeutic miRNAs, siRNAs, or neuroprotective proteins represent an emerging modality that leverages EVs' natural capacity for blood-brain barrier crossing and intercellular communication (Shahlaei et al., 2025). This approach offers the advantage of utilizing the body's endogenous delivery system while potentially avoiding some of the immunogenicity and off-target effects associated with synthetic nanoparticles. DS-relevant rodent models, including trisomic mouse strains such as Ts65Dn and Dp16, provide valuable translational platforms for preclinical testing of both miRNA-targeted and EV-based therapeutic interventions (Farrell et al., 2022).

Biomarker Development and Clinical Translation

EV miRNA/Protein Panels for Early Detection

The detectability of brain-derived miRNA and protein signatures in peripheral blood EVs positions them as candidate biomarkers for preclinical AD detection in DS. The minimally invasive nature of blood-based biomarkers offers significant advantages over CSF sampling or neuroimaging for routine screening and longitudinal monitoring, particularly in DS populations where cognitive assessment can be confounded by baseline intellectual disability. However, longitudinal studies with adequate sample sizes are needed to establish temporal dynamics of these molecular signatures and to validate their predictive power for cognitive decline and conversion to clinical dementia (Pham et al., 2024; Park et al., 2024).

Challenges in Standardization

Translating EV biomarkers from research settings to clinical use requires addressing substantial pre-analytical and analytical variability. Standardization of isolation methods—including ultracentrifugation, size-exclusion chromatography, and immunocapture approaches—is essential, as different techniques yield EV preparations with varying purity and subpopulation composition. Storage conditions, sample handling protocols, and normalization strategies for miRNA and protein quantification must also be harmonized across laboratories to ensure reproducibility and enable multi-center biomarker validation studies. The development of standardized reference materials and quality control metrics represents a critical step toward clinical implementation of EV-based diagnostics (Bravo-Miana et al., 2024).

Future Directions and Limitations

Current evidence derives largely from cross-sectional studies with limited sample sizes, which constrains the ability to draw causal inferences and establish temporal relationships between miRNA dysregulation and AD progression. Longitudinal cohort studies are essential to establish miRNA/protein trajectories over time and to validate prognostic biomarkers that can identify DS individuals at highest risk for rapid cognitive decline. Functional mechanistic studies in DS-relevant models, including iPSC-derived neurons and glia from DS individuals as well as trisomic mouse models such as Ts65Dn and Dp16, are needed to dissect cell-type-specific contributions of miRNA dysregulation and to rigorously test therapeutic interventions in controlled settings (Farrell et al., 2022). Multi-omics integration incorporating genomics, transcriptomics, proteomics, metabolomics, and neuroimaging will enable construction of

systems-level models of DS-AD pathogenesis that capture the complexity of gene-dose effects, regulatory network perturbations, and their downstream consequences on brain structure and function. Ultimately, clinical trials of miRNA-targeted or insulin-sensitizing therapies in DS populations at risk for or in early stages of cognitive decline will be required to translate mechanistic insights into disease-modifying treatments that can delay or prevent the near-universal progression to AD in this vulnerable population.

Conclusion

The convergence of chromosome 21 gene dosage effects, inflammatory miRNA dysregulation, and metabolic dysfunction create a multifaceted vulnerability to Alzheimer's disease in Down syndrome. Extracellular vesicle-derived miRNA-protein networks reveal miR-155 as a central regulatory node linking neuroinflammation to neuronal insulin resistance and synaptic impairment. These findings support the development of EV-based biomarker panels for early detection and disease monitoring and highlight miRNA-targeted and metabolic therapies as promising strategies for modifying DS-associated AD trajectories. Continued integration of molecular profiling with functional validation and clinical translation will be essential to realize the therapeutic potential of these insights.

Acknowledgement

I would like to express my sincere gratitude to our Honorable Chairman, Vice-Chancellor, Chief Operating Officer, Dean, and Director of the School of Life Sciences, as well as the other esteemed authorities of Swami Vivekananda University, for their constant support and encouragement. I am also deeply thankful to the Head of the Department of Microbiology and Biotechnology, School of Life Sciences, Swami Vivekananda University, for providing me with this valuable opportunity to carry out the present study.

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